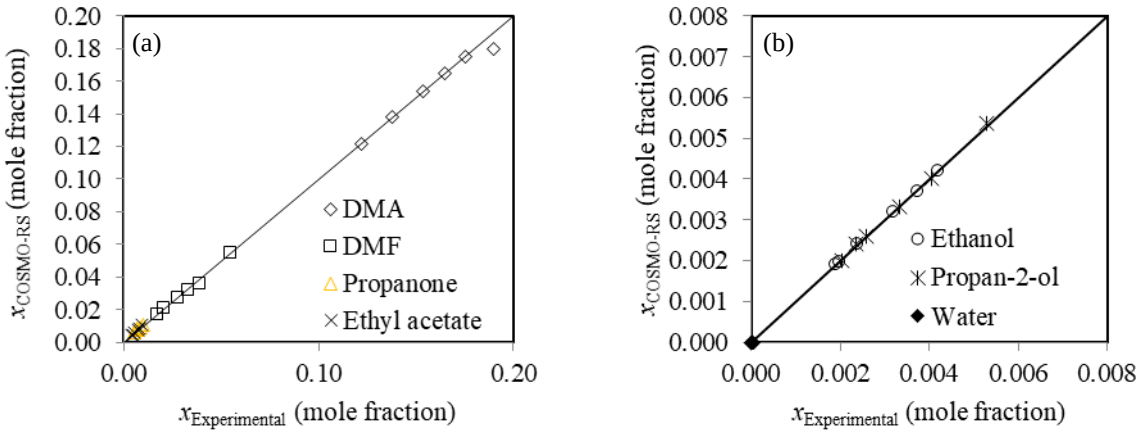
Prediction of Mefenamic Acid Solubility and Molecular Interaction Energies in Different Classes of Organic Solvents and Water

S. K. Abdul Mudalip,[1] F. Adam,[1] M. R. Abu Bakar,[2] P. Jamal[3]

[1] *Faculty of Chemical & Natural Resources Engineering, Universiti Malaysia Pahang, 26300 Gambang, Pahang, Malaysia.*
[2] *Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia.*
[3] *Department of Biotechnology Engineering, Kulliyyah of Engineering, International Islamic University Malaysia, 50728 Kuala Lumpur, Malaysia.*
*Corresponding author: kholijah@ump.edu.my

Extended Abstract

Solubility of a targeted compound as a function of temperatures or solvent compositions is essential in designing pharmaceutical crystallization process [1, 2]. Due to that, fast determination of solubility data either through experimental or model based approaches becomes a necessity. Mefenamic acid (2-[(2,3-dimethylphenyl)amino]benzoic acid, $C_{15}H_{15}NO2$) is extensively used for control of pain due to menstrual disorder and as anti-proliferative agents [3]. Conductor-like Screening Model for Real Solvents (COSMO-RS) is an alternative method for prediction of thermodynamics properties of fluids based on the molecular charge density that obtained by molecular quantum chemical calculation (COSMO) [4]. The aim of this work is to predict and investigate the solubility of mefenamic acid as a function of solvent types and temperatures using COSMO-RS. The solvents studied in this work were divided into three groups. Group 1 comprises of dipolar aprotic solvents (N, N-dimethylacetamide (DMA), N, N-dimethylformamide (DMF), acetone and ethyl acetate). Group 2 consist of polar protic solvents (ethanol, propan-2-ol, and water). Group 3 consist of apolar aprotic solvents (hexane, heptane, and cyclohexane). The temperatures were varied from 298 K to 323 K. The mefenamic acid show high solubility in solvent form Group 1, moderate in Group 2, except water and poor in Group 3. As illustrated in Fig. 1, the predicted solubility values using COSMO-RS concur very well with the experimental values obtained from literature [5] with an average mean relative errors (mse) less than 0.02. The predicted solubility also increase with the increase of the temperature. The calculated Gibbs free energy change of mefenamic acid in the solvents studied also agreed with the solubility data. The increase of solubility with the increase in temperature is probably due to the increase in molecules' kinetic energy at higher temperatures that leads to more effective movement or interactions between solvents with the solute molecules. Moreover, the heat adsorbed at high temperature facilitate the dissolution of solute compound by breaking the bonds in the solute molecules [6]. The predicted microscopic interaction energies, namely misfit (H-MF), hydrogen bonding (H-HB), and van der Waals (H-vdW) show small increment in the energies values as the temperature increases. The changes of H-HB energy in different solvents are more significant than H-vdW and H-MF (See Fig. 2). This findings may suggest that the H-HB interactions between mefenamic acid and solution are significantly contribute to the differences in the mefenamic acid solubility.



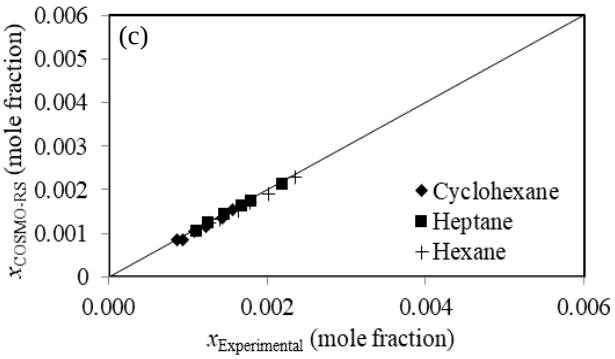


Fig. 1: Comparison of mefenamic acid solubility values predicted using COSMO-RS and literature [5] in different classes of organic solvents. Mefenamic acid was assumed as a subcooled liquid and do not form an ideal solution in the solvents studied: (a) Group 1: DMA, DMF, propanone and ethyl acetate (dipolar aprotic); (b) Group 2: Ethanol and propan-2-ol (polar protic); and (c) Group 3: Cyclohexane, heptane and hexane (Apolar aprotic).

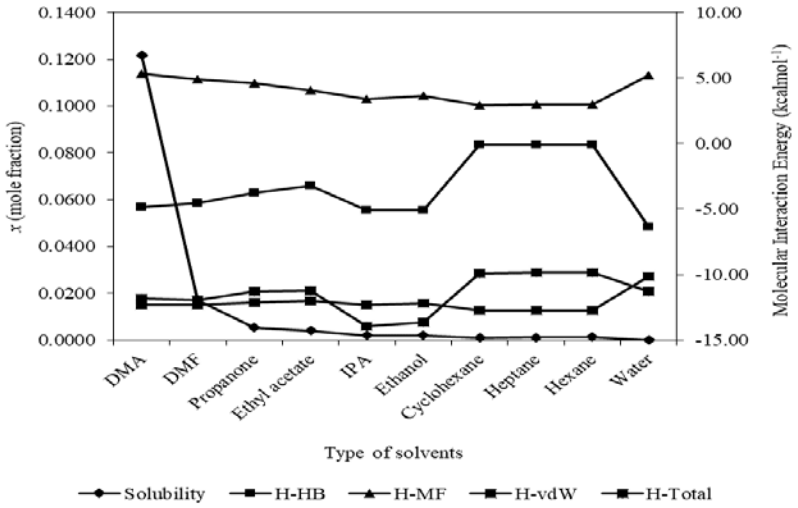


Fig. 2: Microscopic energies of mefenamic acid in different solvents at 298 K.

Keywords: COSMO-RS; Solubility, Intermolecular interactions, Gibbs energy.

Acknowledgment

This work was financially supported by Ministry of Higher Education Malaysia and Universiti Malaysia Pahang (Exploratory Research Grant Scheme RDU120607 and RDU150359). The authors are grateful to F. Eckert and A. Klamt, COSMOtherm, Version C3.0, Release 13.01; COSMOlogic GmbH & Co. KG, Leverkusen, Germany, 2013 for their technical support.

References

[1] Bennet, R. C. (2007). Crystallizer Selection In A. S. Myerson (Ed.), Handbook of Industrial Crystallization (pp. 115-140). Butterworth-Heinemann, USA.
[2] He, Y., Ho, C., Yang, D., Chen, J., Orton, E. (2017). Measurement and Accurate Interpretation of the Solubility of Pharmaceutical Salts. J. Pharm. Sci., 106(5): 1190-1196.
[3] Cesur, S., Gokbel, S. (2008). Crystallization of mefenamic acid and polymorphs. Cryst. Res. & Technol. 43: 720-728.
[4] Eckert, F., Klamt, A. (2002). Fast solvent screening via quantum chemistry: COSMO -RS approach. AIC 369-385.
[5] Abdul Mudalip, S. K., Abu Bakar, M. R., Jamal, P., Adam, F. (2013). Solubility and dissolution thermodynamic data of mefenamic acid crystals in different classes organic solvents. J. Chem. Eng. Data. 58: 3447-3452.
[6] Zhang, T., Liu, Q., Xie, Z., Song, X., Gong, J. (2014). Determination and correlation of solubility data and dissolution thermodynamic data of cefixime trihydrate in seven pure solvents J. Chem. Eng. Data., 59(6), 1915-1921.